Diagnosis and management of chronic obstructive pulmonary disease: the swiss guidelines. Official guidelines of the Swiss Respiratory Society

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Abstract: The new Swiss Chronic Obstructive Pulmonary Disease (COPD) Guidelines are based on a previous version, which was published 10 years ago. The Swiss Respiratory Society felt the need to update the previous document due to new knowledge and novel therapeutic developments about this prevalent and important disease. The recommendations and statements are based on the available literature, on other national guidelines and, in particular, on the GOLD (Global Initiative for Chronic Obstructive Lung Disease) report. Our aim is to advise pulmonary physicians, general practitioners and other health care workers on the early detection and diagnosis, prevention, best symptomatic control, and avoidance of COPD as well as its complications and deterioration.

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Management of Chronic Obstructive Pulmonary Disease

The Swiss Guidelines

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1 Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of chronic morbidity and mortality throughout the world. Its prevalence and its social as well as economic burden are increasing due in part to the aging of the population. According to the Global Burden of Disease Study (BOLD) COPD is projected to rank fifth worldwide as cause of death in the year 2020 [1]. COPD is related in many cases but not exclusively to cigarette smoking, and in some areas of the world with large populations, air pollution resulting from the burning of biomass fuels has been identified as a relevant risk factor [2, 3].

Over the past years the COPD guidelines of various national and professional associations have been revised [4-7] and in December 2011, ten years after its first release, the third and updated version of the GOLD report (Global Strategy for Diagnosis, Management and Prevention of COPD) has become available [8]. Our present guidelines are based on a previous version 2002 [9] and consider new knowledge and novel developments. They aim to advise pulmonary physicians, general practitioners, and other health care workers on the early detection and diagnosis, the prevention, the best symptomatic control, the avoidance of complications and deterioration of COPD.

1.1 Definition

COPD is characterized by chronic airflow limitation and a range of pathological changes in the lung, significant extrapulmonary effects and important comorbidities, which may contribute to the severity of the disease in individual patients (GOLD updated 2011) [8]. The chronic airflow limitation is caused by an individual mixture of small airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema). Chronic bronchitis is a clinical and epidemiological term and is defined by a history of cough and mucus production on most days for at least three months a year during at least two successive years. Not all patients with chronic bronchitis also have COPD, and not all patients with COPD suffer from symptoms of chronic bronchitis.

1.2 Pathophysiology

The major risk factors for the development of COPD are inhaled toxic substances, particularly the inhalation of tobacco smoke and burning products of biomass fuels that cause inflammation of the lungs. The inflammation can lead to tissue damage if the normal

protective and/or repair mechanisms are overwhelmed or defective. The results of the lung tissue damage are mucus hypersecretion, airway narrowing, and fibrosis, destruction of the parenchyma and vascular changes. These pathological changes lead to airflow limitation, loss of elastic recoil and other physiological abnormalities. The inflammation in COPD is markedly different from that in asthma. However, some patients with COPD also have asthma and the inflammation in their lungs may show characteristics of both diseases. Since inflammation is a feature of COPD, anti-inflammatory therapies may have beneficial effects in controlling symptoms, preventing exacerbations, and slowing disease progression. However, the response of inflammation to corticosteroids is poor in COPD contrary to their effectiveness in asthma.

1.3 Risk factors

COPD arises from an interaction of both host factors and environmental exposures. Smoking remains a leading cause for COPD. It is estimated, that in industrialized countries in men about 80% and in women around 60% of the COPD mortality is attributable to smoking, whereas in developing countries smoking contributes to only about 45% in men and 20% in women [10, 11]. In unindustrialized countries biomass fuel utilization for cooking and heating at home is an important environmental factor. Other factors may include occupational exposures, second hand smoking, and outdoor air pollution. The population-attributable fraction for the work-place contribution to COPD risk has been estimated to be 15% to 20% in Europe and North America [10]. The risk in less regulated areas of the world is likely to be much higher. In the SAPALDIA study high levels of occupational exposures to biological dusts, mineral dusts, gases or fumes, as determined from self-reported occupational exposure, were found to be associated with increased incidence of COPD stage $\geq$ 2 [12].

Host factors include genetics, epigenetics, and other characteristics of the host such as bronchial hyperreactivity, a history of asthma [13], as well as a history of severe respiratory infection in childhood. Inherited alpha-1-antitrypsin deficiency is a single gene autosomal recessive disease that predisposes to COPD, but that accounts for less then 1 % of all cases of COPD [14, 15]. Apart of this particular gene, genetic predisposition to COPD is much more complex and is incompletely understood at the moment. COPD has been associated with polymorphisms of various genes, but very few of these associations have been replicated in more than two or three independent population samples [16]. Other factors may also predispose to the development of COPD. Bronchial hyperreactivity is a risk factor even after

exclusion of asthmatics [17,18] and chronic bronchitis symptoms seem to increase the risk for the later development of COPD [19,20].

1.4 Epidemiology and burden of disease

COPD prevalence data show remarkable variation due to differences in survey methods and diagnostic criteria. The Burden of Obstructive Lung Disease (BOLD) study reports between-countries variability in prevalence of GOLD stage 2 to 4 COPD [21], ranging from 9% in Iceland to 19% in the Philippines for male subjects aged more than 40 years old. Country-specific age distributions, smoking prevalence rates and other important environmental factors may contribute to most of these disparities. In Switzerland, in a sample of 6'126 subjects (SAPALDIA), the prevalence of COPD GOLD stage $\geq$ 2 was 5.1% in the population aged 30 to 73 years and the prevalence of stage $\geq$ 1 was 10% [22]. Prevalence was strongly dependent on the age. Consequently, extrapolated to a resident population of 7.8 million in Switzerland (2010 census), the estimated number of stage $\geq$ 2 COPD ranges between 200'000 and 300'000, and of $\geq$ 1 COPD about 400'000.

1.5 Assessment

1.5.1 Clinical assessment

Although an important part of patient care, physical examination has a low sensitivity and specificity for the detection or exclusion of mild to moderately severe forms of COPD. If physical signs of airflow obstruction and pulmonary hyperinflation are present, the patient usually suffers from an advanced stage of the disease. The leading symptoms of COPD are shortness of breath during exercise, exercise limitation and chronic cough [23]. The degree of dyspnea can be assessed by the Modified Medical Research Council questionnaire (mMRC) [24] (table1). The COPD Assessment Test (CAT) [25] has a broader coverage of the impact of COPD on the patient's daily life and well-being and correlates closely with health status measured using the St.Georges Respiratory questionnaire. The test is translated in several languages, contains 8 items and can be easily performed on the internet www.catestonline.org (table 2). Another important element of a patient's history is the occurrence and frequency of exacerbations. An exacerbation of COPD is defined as an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication. The exacerbation rate varies greatly between patients. The best predictor of having frequent exacerbations ($\geq$ 2 per year) is a history of previous

exacerbations and the severity of COPD [26]. Since COPD often develops in middle-aged long-time smokers, patients frequently have a variety of other diseases related to either smoking or aging. Comorbidities that occur frequently in COPD patients include cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, lung cancer and depression [27]. The comprehensive assessment of a patient with COPD forms the basis for therapy and combines the symptomatic assessment with the patient's spirometric classification and/or the risk of exacerbations.

The degree of airflow obstruction, as assessed by the FEV1 is but one of the essential prognostic features of COPD. Several studies have shown, that in addition the severity of dyspnea, walking distance and body mass index (BODE index, table 3) correlate best with life expectancy in COPD [28].

1.5.2 Pulmonary function testing

Lung function should be tested in patients with symptoms of COPD, such as chronic cough, wheezing, shortness of breath and limitation on exertion. Clinicians should however be alert that some patients may deny exertion limitation because they have spontaneously reduced their habitual level of activity [29]. Spirometry is the gold standard to assess the presence and degree of airflow obstruction. The abnormalities consist of a reduction in FEV_1 and in the ratio of FEV_1 to the forced vital capacity (FVC). Small, handheld spirometers are convenient to use, have a graphic display, store, and print the numeric results as well as the flow-volume curve or the spirogramm of the patient. Office spirometry should be performed in primary care by well-trained personnel [30, 31]. In COPD the correlation between peak expiratory flow (PEF) and FEV_1 is poor. Therefore, the measurement of PEF, well established in the management of asthma, should not be used in patients with COPD. The degree of airflow obstruction in COPD is classified as proposed by GOLD (table 4). This arbitrary international staging system is intended to standardize the diagnosis of COPD by using a fixed threshold of $FEV_1/FVC < 0.70$ for airflow obstruction and to grade its severity based on FEV_1 as percent of predicted. However, since the FEV_1/FVC ratio declines physiologically with age, using a fixed ratio of 0.70 instead of the lower limit of normal (LLN), leads to COPD overdiagnosis in older subjects, particularly for GOLD stage 1. In Switzerland, the SAPALDIA study showed that among individuals classified as GOLD stage I COPD, only the subjects manifesting cough, phlegm or dyspnoea had a faster decline in FEV_1, increased respiratory care utilization, and impaired quality of life. In contrast, asymptomatic individuals classified

as stage I COPD did not differ from subjects with normal lung function [20]. Thus, for subjects with lung function corresponding to GOLD stage I, a cautious approach would consider the diagnosis of COPD only in those manifesting symptoms of the disease. When provided by the spirometer, the use of LLN for FEV_1/FVC is a physiologically sound alternative which reduces the misclassification of airway obstruction [32-34]. Bodyplethysmography is used to measure intrathoracic gas volume for the calculation of residual volume (RV) and total lung capacity (TLC), parameters that reflect pulmonary hyperinflation. Diffusing capacity for carbon monoxide is measured by the single breath technique. These parameters correlate with the degree of emphysema and it is therefore recommended that plethysmography is performed on a regular base for follow-up in patients with severe COPD that may benefit from a lung volume reduction procedure.

1.5.3 Chest X-ray and Thoracic CT scan

A chest radiograph is indicated as part of the initial workup of patients with COPD to exclude concomitant pathologies. However, chest films are not sensitive for the detection of mild to moderate emphysema. High resolution computed tomography (HRCT) is the most sensitive and specific in vivo technique for the detection, grading and morphological characterizing of pulmonary emphysema. While CT scanning is not recommended for routine clinical assessment of COPD, it may be used to evaluate alternative diagnosis and to assess the feasibility of lung volume reduction surgery.

1.5.4 Further Assessment

Hypoxemia is an important problem in COPD, accentuates intolerance to physical exercise and adds to its morbidity. Exercise tests such as the 6-minute walk test or in selected cases spiroegometry should be performed with continuous oxygen saturation measurements. If pulsoxymetry at rest shows a saturation of < 92% an arterial blood gas analysis should be performed. If erythrocytosis is present chronic hypoxemia should be suspected. Measurement of the α-1 antitrypsin serum concentrations is indicated in rapidly deteriorating COPD, in patients with COPD at an age below 45 years and in cases with emphysema of basal predominance. In case of increased daytime sleepiness, oximetry at night or respiratory polygraphy may be indicated to rule out hypoxemia during sleep or an overlap syndrome (COPD an obstructive sleep apnea).

2 Management of COPD

2.1 Prevention

Identification, reduction, and control of risk factors such as tobacco smoke, occupational exposure and in- and outdoor pollution are important steps to prevent the development of COPD. Smoking cessation is the single most effective intervention with the greatest impact on the natural history of COPD [35,36] (Evidence A). Brief advice by a general practitioner results in smoking cessation rates of 7.4 %, i.e. an increase of 2.5% over the cessation rate in a control group, and counseling of 3 to 10 minutes duration achieves higher cessation rates of around 12 %. With greater investment of time and complexity of interventions, including skills training, problem solving and psychosocial support, the quit rate can reach 20% to 30% [37] (Evidence A). In the Lung Health Study, a multicenter controlled clinical trial, a combination of advice by a physician, group support, skills training and nicotine replacement therapy achieved quit rates of 35 % at one year and sustained quit rates of 22 % at 5 years [38]. Pharmacotherapy is effective in supporting smoking cessation attempts and at least one of these substances should be prescribed in the absence of contraindications: varenicline, bupropion SR and nicotine in various galenic preparations [39-44] (Evidence A). Occupationally induced respiratory disorders, e.g. in farmers, can be reduced or controlled by strategies aimed at reducing the burden of inhaled particles and gases at the workplace [46] (Evidence B).

2.2 Patient Education

Patient education is effective in accomplishing specific goals, including smoking cessation [38] (Evidence A), initiating discussion and understanding of advanced directives and end of life issues [46] (Evidence B) and improving patients' responses to exacerbations [47] (Evidence B), e.g. by implementing written action plans.

2.3 Pharmacologic treatment

None of the available medications for COPD are effective in modifying the long-term progression of airflow limitation that is the hallmark of this disease (Evidence A). Today's polypharmacy, overuse, and overdose of medications are a significant burden to the cost of COPD management.

2.3.1 Bronchodilators

Bronchodilator medications are given on either an as-needed basis or a regular basis to prevent or reduce symptoms of COPD (Evidence A). They have the potential to improve exhalation, to reduce dynamic hyperinflation, improve exercise performance and decrease shortness of breath. However, they do not modify the decline of lung function and by inference, the prognosis of the disease (Evidence B). They are given on an as needed or on a regular basis based on severity of COPD. Aerosol formulations are the preferred way of administration. Attention to effective drug delivery and training in inhalation technique is essential. The use of metered dose inhalers (MDI) with spacer devices, dry powder inhalers (DPI) or possibly of nebulizers should be tailored to the patient's ability. The choice between β_2-agonists or anticholinergics or a combination therapy depends on individual patient response in terms of symptom relief and side effects. Long-acting inhaled bronchodilators are convenient and more effective of producing maintained symptom relief than short-acting bronchodilators.

Anticholinergics

The inhibition of vagal stimulation of the bronchial tree is associated with reduced smooth muscle tone and bronchial gland secretion. The bronchodilating effect of short-acting inhaled anticholinergics lasts up to 8 hours after administration (Evidence A). Tiotropium is a long-acting anticholinergic bronchodilator, which has to be inhaled only once daily [48]. It reduces exacerbations and related hospitalizations, improves symptoms and health status [49] (Evidence A). In a large, long-term clinical trial (UPLIFT) [50], there was no effect of tiotropium added to other standard therapies on the rate of lung function decline and no reduction in mortality. In another large trial, tiotropium was superior to salmeterol in reducing exacerbations although the difference was small [51] (Evidence A).

In 2008 a meta-analysis of 17 randomized trials reported an increased risk of cardiovascular events by the use of anticholinergics [52]. In contrast the UPLIFT trial [50] did not show an increased risk. A FDA expert panel discussed these contradictory findings and concluded, based on methodological considerations, that the current data do not support the supposition that the use of tiotropium is accompanied by an increased risk of cardiovascular events [53].

Beta$_2$-agonists

Sympathomimetic bronchodilators protect against bronchospasm induced by various stimuli, reduce static and dynamic hyperinflation and improve dyspnea even if FEV_1 remains unchanged. The effects of short-acting beta-agonists (SABA: salbutamol, terbutaline or formoterol) disappear within 4 to 6 hours. SABAs are used as rescue medication and patients are allowed to increase the number of puffs and to shorten the interval between puffs from MDI or DPI up to 3-4 hours, provided it is for a short period of time.

The effects of long acting inhaled β_2-agonists (LABA: salmeterol and formoterol) are maintained over 12 hours or even for up to 24 hours by the ultra-long acting bronchodilator indacaterol, which needs to be administered only once daily [54,55].

In the TORCH trial studying the combined effect salmeterol and fluticasone [56], the lung functions, the number of exacerbations and the average change in clinical scores over 3 years was significantly better in the combination therapy group than in the salmeterol-alone group, the fluticasone-alone group, and the placebo group. The side effects of β_2-agonists are proportional to their dosage and consist mostly of a tremor, some degree of tachycardia, and hypokalaemia especially when prescribed with diuretics.

2.3.2 Phosophodiesterase-Inhibitors

Theophylline is a xanthine derivate and acts as a nonselective phosphodiesterase inhibitor. It has a modest bronchodilator effect in stable COPD (Evidence A) [57] and shows various physiologic actions, the significance of which is disputed. Theophylline is metabolized by cytochrome P450-dependent mixed function oxidases and many physiological variables and drugs modify its metabolism. It is less effective and less well tolerated than inhaled long-acting bronchodilators and is therefore not recommended as first line drug.

Roflumilast is a phosphodiesterase-4 inhibitor and has recently been approved for use in COPD GOLD stage III and IV. Its principal action is to reduce inflammation by inhibiting the breakdown of intracellular cyclic AMP. Roflumilast reduces moderate and severe exacerbations by 15-20% in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations (Evidence A) [58, 59]. It is a once daily medication and slight improvements in FEV_1 are seen when roflumilast is added to long-acting bronchodilators.

There are no comparison or add-on studies of roflumilast and inhaled corticosteroids. Patients have to be informed about the potential side effect consisting of diarrhea and weight loss.

2.3.3 Glucocorticosteroids

When considering the position of glucocorticosteroids in the management of COPD, their role during exacerbations and during stable phases of COPD (steroid trial) should be distinguished. The effects of glucocorticosteroids on airway inflammation in COPD are much less pronounced than in asthma. Based on the lack of any evidence of a long-term beneficial effect of chronic oral glucocorticoid therapy in subjects with confirmed COPD and a large body of evidence on the long-term adverse effects of this treatment, chronic treatment with oral glucocorticosteroids should be avoided in COPD [60-64] (Evidence A).

Steroid trial

A short course of oral corticosteroids is not a reliable predictor of the long-term response to inhaled glucocorticosteroids in COPD [65]. However, short course of oral corticosteroids are indicated in COPD exacerbation (s. exacerbation) and to differentiate COPD from bronchial asthma. The results of a steroid trial can only be assessed in a stable phase of the disease, at least 6 weeks after an exacerbation and based on repetitive and reproducible measurements of the patients FEV_1.

Inhaled glucocorticosteroids

The dose-response relationships and long-term safety of inhaled corticosteroids (ICS) in COPD are not known. Only moderate to high doses have been used in long-term clinical trials. The effects ICS on pulmonary and systemic inflammation in patients with COPD is controversial. ICS, particularly in fixed combinations with LABA are overused and their role should be limited to specific indications. Regular treatment with ICS does not modify the long-term decline of FEV_1 nor mortality in patients with COPD (Evidence A). ICS improve symptoms, lung function, quality of life and reduces the frequency of exacerbations in COPD patients with a $FEV_1 < 60\%$ predicted (Evidence A). ICS in combination with a LABA is more effective than the individual components in improving lung function, health status and reducing exacerbation with moderate (Evidence B) to very severe COPD (Evidence A). In summary, the use of ICS is recommended in severe and very sever COPD and in COPD GOLD stag II with an FEV1 < 60% pred. and frequent exacerbation. Combination therapy

was associated with an increased risk of pneumonia, but no overall mortality in the TORCH trial (Evidence A) [56, 66-72]

The addition of a LABA/ICS combination to tiotropium is frequently used in severe to very severe COPD. This combination improves lung function and quality of life and may further reduce exacerbations [73, 74].

2.3.3 Antibiotics

The use of antibiotics in stable disease (i.e. outside exacerbations) is not recommended. A recent trial of daily azithromycin, a macrolide antibiotic, showed efficacy on exacerbation end-points [75]. However, its use is not recommended until further studies confirm its effectiveness and exclude relevant long-term side-effects.

2.3.4 Mucolytics

A review article has been published recently about the effects of mucoactive therapy in COPD [76]. The majority of the trials have been performed with N-acetylcysteine and carbocysteine. Overall the authors found a significant reduction in exacerbations and the number of days with disability. Mucolytics were well tolerated and the number of adverse events was lower than with placebo. However, in the largest and best designed study with N-acetylcysteine in 523 patients with COPD, the reduction in exacerbations was only observed in patients not taking inhaled corticosteroids [77]. The use of mucolytics is not generally recommended, but may be an option in COPD patients with frequent exacerbations.

2.3.5 Immunoregulators

Immunstimulating agents made from bacterial extracts represent a class of medications whose potential benefit results from a nonspecific stimulation of the immune system.
A systematic review of the studies over the use of bacterial extracts in COPD patients has showed reduction in symptoms of COPD exacerbations but no reduction of exacerbation rate [78].

2.4 Vaccination

2.4.1 Influenza vaccination

Influenza vaccination can reduce lower tract respiratory infections requiring hospitalization

and death (Evidence A) [79]. Vaccination does not increase consultations, corticosteroid prescriptions or exacerbations in subjects with asthma or COPD [80, 81]. The strains are adjusted each year for appropriate effectiveness and should be given each year in autumn (or eventually twice, in autumn and winter).

2.4.2 Pneumococcal vaccine

The 23-valent pneumococcal polysaccharide vaccine protects against invasive pneumococcal disease, such as bacteremia and meningitis, but does not reduce all-cause pneumonia. In a small study a decreased rate of pneumonia was found only in younger persons (<65 years) and in those with severe airflow obstruction (FEV_1< 40%) [82]. In spite of this weak evidence the 23-valent pneumococcal polysaccharide vaccine is recommended for all persons with chronic lung disease (Evidence B). Results on the effect of a conjugated 13-valent pneumococcal vaccine in adults are not available for the time being.

2.5 Oxygen therapy

It has been shown that the survival of patients with chronic respiratory failure due to COPD is improved by long-term O_2 administration (> 15 hours per day) (Evidence B) [83-85].
Long-term oxygen therapy [86] is indicated if the PaO_2 is:

- at or below 7.3 kPa (55 mm Hg) with or without hypercapnia confirmed twice over a three week period (Evidence B), or
- between 7.3 kPa (55 mm Hg) and 8.0 kPa (59 mm Hg), if there is evidence of pulmonary hypertension or polycythemia (hematocrit > 55%) (Evidence D).
- situative hypoxemia, i.e. hypoxemia (<90% saturation) during sleep or during exercise.

The primary goal of oxygen therapy is to increase the baseline arterial partial pressure (PaO_2) to at least 8.0 kPa (60 mm Hg) or to achieve arterial oxygen saturation equal to or above 90 %. Smoking cessation is a requirement for long-term oxygen therapy. The prescription of oxygen should always include the source of supplemental oxygen (gas or liquid), the method of delivery (nasal cannula, transtracheal), duration of use (> 15 hours or, if possible 24 hours per day), and the flow rate at rest, during exercise and sleep. Oxygen given during exercise may increase walking distance and endurance most likely by optimizing oxygen delivery to tissues and its utilization by muscles. However, there are no data to suggest that long-term oxygen therapy changes exercise capacity per se.

In the absence of symptoms of sleep apnea, there is no indication for specific sleep studies.

2.6 Alpha-1-antitrypsin replacement

Intravenous replacement with α1-antitrypsin (ATT) increases AAT levels and anti-elastase activity in serum and in bronchoalveolar lavage fluid [15]. Uncontrolled trials have shown positive effects with augmentation therapy. Two small randomized, double-blind, placebo-controlled trials have investigated the efficacy of intravenous AAT augmentation therapy on emphysema progression using CT densitometry [87, 88]. Data from these similar trials, the 2-center Danish-Dutch study (n = 54) and the 3-center EXACTLE study (n = 65), have been pooled to increase the statistical power [89].All subjects, 60 under replacement and 59 in the placebo group were assessed by a CT scan at baseline and after treatment with a mean follow-up of approximately 2.5 years. The combined data, as analyzed by one of four analytical methods, showed a significantly reduced decline in lung density. However, clinical endpoints (decline of FEV_1, exacerbation rate, quality of life) did not reach statistical difference. Therefore and due to a lack of accepted criteria to assess the efficiency of this costly treatment, a recommendation for AAT replacement cannot be given.

2.7 Ventilatory support

Non-invasive ventilation in combination with long-term oxygen therapy may be used in a selected subset of patients, particularly in those with pronounced daytime hypercapnia. In patients with both COPD and obstructive sleep apnea there are clear benefits from continuous positive airway pressure (CPAP) in both survival and risk of hospital admission [90, 91].

2.8 Pulmonary rehabilitation, psychological support and nutrition

2.8.1 Rehabilitation

Exercise capacity and the level of physical activity are strong prognostic factors in COPD. Pulmonary rehabilitation and maintenance of physical activity have the potential to improve exercise tolerance, to decrease dyspnea and anxiety and to reduce the number of hospitalizations [92, 93] (Evidence A). Comprehensive pulmonary rehabilitation includes patient education, nutritional counseling and exercise training. The type of exercise (stair climbing, walking, treadmill, bicycle ergometer) may vary and is best determined by patient preference. Interval exercise training is usually better tolerated by patients. Whether

pulmonary rehabilitation is done in an in- or outpatient program depends on local availability, patient's preference and comorbidity. Pulmonary rehabilitation is also effective soon after exacerbations [94]. Comorbidities are not a contraindication for pulmonary rehabilitation [95]. The benefit in exercise performance and quality of life is maintained, if patients follow a regular exercise program at home [96]. The routine use of respiratory muscle training cannot be recommended, but individual patients may benefit.

2.8.2 Psychological support

COPD is a progressive disease that eventually will severely impair the patient's quality of life. Even with the best care shortness of breath, already occurring during daily activities, profoundly modifies family life, sexuality, and social interaction. The patient becomes more isolated, dependent, and full of grief. This complex burden of suffering can be overwhelming. The patient's coping mechanisms may be insufficient. Prevalence of anxiety and depression is higher in some groups of COPD patients and is associated with dyspnea and reduced quality of life [97-99]. Exercise training and antidepressant drugs are often effective in amelioration dyspnea and anxiety [100]. Pulmonary rehabilitation may decrease psychosocial morbidity even without specific psychological intervention [101].

2.8.3 Nutrition

Weight loss is a common feature in patients with advanced COPD The clinical importance of weight loss, particularly of fat-free mass (FFM), and in its adverse effects on physical performance and quality of life has been demonstrated [102]. Moreover, a low body mass index (BMI) is an independent predictor for increased mortality [103]. Although nutritional support in these patients seems logical, controlled trials have not shown significant effects of weight gain on lung function or exercise capacity in patients with stable COPD [104]. The supplementation may however improve the outcome of training in some patients [105].

2.9 Invasive interventions

2.9.1 Lung volume reduction surgery

Bullectomy i.e. the removal of large bulla that compresses the adjacent lung structures is a well-established surgical procedure and can be performed thoracoscopically. It is effective in reducing dyspnea and improving lung function [106,107]. Lung volume reduction surgery (LVRS) reduces emphysematous parts of the lung to reduce hyperinflation. It is a palliative procedure which does not only improve pulmonary function and exercise capacity in selected patients with severe hyperinflation, but has a major positive impact on quality of life for

several years [108,109]. Patients with heterogeneous types of emphysema and low exercise capacity have the greatest improvement in pulmonary function after LVRS [110], but also patients with homogeneous emphysema may also experience significantly better health status and lung function as compared to usual medical care, when high risk candidates with an extremely low FEV1 and a homogeneous emphysema or a diffusing capacity < 20% predicted were excluded.

2.9.2 Bronchoscopic lung volume reduction

A range of different techniques such as endobronchial valves, coils, airway bypass, thermal vapor ablation and biological sealants have been employed in both homogeneous as well as heterogeneous types of emphysema. Carefully selected patients with very severe COPD may benefit from bronchoscopic lung volume reduction [111]. However, the currently available data on efficacy and safety of different types of bronchoscopic lung volume reduction procedures are not conclusive and further data is therefore needed.

2.9.3 Lung transplantation

The decision to proceed with lung transplantation for severe COPD is complex. Plenty evidence suggests that functional capacity is improved following the procedure, but the presence of a survival benefit is less clear. It is important to define disease severity as precisely as possible in order to determine which patients have the most urgent need for lung transplantation and are likely to have the longest survival after transplantation. Transplantation is usually deferred until the BODE index is seven or higher, the FEV_1 is below 20 percent of predicted, the diffusing capacity for carbon monoxide is below 20 percent of predicted or the clinical course becomes more aggressive with life-threatening exacerbations. Since many patients with advanced COPD are of older age and affected by various comorbidities the selection of suitable transplant candidates is a particular challenge. Contraindications for lung transplantation are malignancies, renal failure or liver failure, drug abuse and emotional instability. It is essential to refer possible lung transplantation candidates early enough for evaluation to a lung transplant center [112-114].

3 Exacerbation of COPD

3.1. Definition, impact, severity, etiology

An exacerbation, defined by the Global initiative for chronic Obstructive Lung disease (GOLD), is „an event in the natural course of the disease characterized by a change in the patients baseline dyspnoea, cough and/or sputum that is beyond normal day to day variation, is acute in onset and may warrant a change in regular medication in a patient with underlying COPD“ [115]. Exacerbations in COPD are characterized by a broad variation in clinical presentation and triggered by several factors.

It has been recognized that there is a subgroup of COPD patients who experience an above normal number of exacerbations, e.i. frequent exacerbators (≥ 2 exacerbations/year). Recurrent exacerbations have a strong negative impact on quality of life, lead to often hospitalizations and are associated with higher rates of morbidity and mortality in COPD. Several clinical features have demonstrated an association with frequent exacerbations, including higher degree of airway obstruction, advanced GOLD stage or BODE category, the presence of chronic cough and sputum production, advanced age and clinical depression.

The current ATS/ERS guidelines provide a descriptive way for defining severity of exacerbations [23]. The classification of exacerbation severity is thereby defined by the necessary extent of the acute medical intervention. Exacerbations are divided in three categories, level 1 with treatment at home, level II requiring hospitalization and level III requiring ICU admission for respiratory failure respectively. The classification of exacerbations in type I-III according to the criteria by Anthonisen et al. [116] does not reflects disease severity but is often used to estimate the likelihood of bacterial cause of COPD exacerbation .

Although less than 50% of exacerbations have a bacterial cause, the presence of bacteria detected by sputum examination varied between 17 % and 87% in cases of COPD exacerbations. In recognition of these diagnostic limitations, sputum cultures should not be performed during most exacerbations. Only selected cases, e.g. patients with FEV1< 30% pred., extensive bronchiectasis, prior evidence of gram negative rods, or contemporary previous antibiotic therapy warrant sputum cultures at exacerbation (Evidence C).

3.2 Therapy

3.2.1 Pharmacological

Bronchodilators, systemic corticosteroids, antibiotic agents, oxygen, and noninvasive positive pressure ventilation are the most common therapeutic measures in exacerbations of COPD.

Bronchodilators

Short-acting β2-agonists are the cornerstone of the treatment of exacerbations of COPD (Evidence D). The addition of an anticholinergic is generally recommended (Evidence D). In contrast, the use of methylxanthines (such as theophylline or aminophylline) is currently considered second line intravenous therapy (Evidence B).

Glucocorticoids

Several randomized, controlled trials suggest that systemic glucocorticoids in COPD exacerbations accelerate recovery of FEV_1, decrease the length of hospital stay and improve clinical outcome (Evidence A) [117]. The strongest treatment effect of steroids occurs probably within the first 72 hour and levels off thereafter suggesting a lack of benefit beyond 5 days of treatment. Despite a lack of well designed randomized trials evaluating the most effective steroid dose, we recommend orally steroids administered once daily in doses of 20 and 60 mg prednisone for 5 to 15 days (Evidence C).

Antibiotics

The role of antibiotics in treatment of COPD exacerbations is much less prominent than the role of steroids [118,119]. Viral infections are known to be the most common cause of acute exacerbations in COPD. Paradoxically, viral exacerbations were associated with more severe exacerbations and prolonged symptom recovery as compared to non- viral exacerbations. However, there is currently no reliable method to clearly distinguish bacterial exacerbations from those caused by other agents. General recommendations for antibiotic use are not uniform and often based on less evaluated clinical parameters Taken the risk of antibiotic overuse into account, routine antibiotic use has to be seen particularly critically in outpatient exacerbations which are often occur with a high spontaneous recovery rate (Evidence C). Antibiotics may be prescribed to patients who have three cardinal symptoms – increase in dyspnea, sputum volume, and sputum purulence (Evidence B), and in patients with severe exacerbation who are admitted to an intensive care unit (Evidence A) [120]. Procalcitonin was shown to reduce the use of antibiotics in COPD exacerbations and may be of value in the

decision to use antibiotics (Evidence A) [121]. If antibiotics are felt to be needed, short treatment course of 5 days or less should be preferred, as they showed equal short- and long term outcome than conventional treatment with antibiotics (7-10 days) (Evidence C) [122]. Longer antibiotics courses should be considered in patients with more severe exacerbations requiring hospital admission or ICU stay and those with proven colonization or infection with gram negative rods.

The effectiveness of older first- line antibiotics (amoxicillin, ampicillin, doxycyclin) and the newer broad-spectrum second line antibiotics (amoxicillin/ clavulanic acid, second and third generation cephalosporin's, quinolones) is comparable regarding mortality, microbial outcome and in the rate of adverse events (Evidence C). Second line agents might present a small benefit in patients with more severe disease or more common exacerbations (Evidence C). Currently, the choice of antibiotic agent should therefore be guided by recent history of antibiotic use and local microbial resistance patterns.

Oxygen

Oxygen therapy should be considered in the treatment of severe COPD exacerbations (Evidence D). Oxygen should be titrated to provide adequate levels of oxygenation (PaO_2 > 8.0 kPa or SaO2 > 90%). It is reasonable to assess arterial blood gases within 30-60 minutes after institution of oxygen therapy to exclude significant CO2 retention.

3.2.2 Non pharmacological

Several randomized trials and meta-analysis indicated that non-invasive positive pressure ventilation (NPPV) improves important clinical outcomes, such as intubation rate, treatment failure and in- hospital mortality in patients having an acute exacerbation complicated by hypercapnic acidosis (Evidence A) [123].

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Tables

Table 1: Modified Medical Research Council Scale (mMRC)

0	No breathlessness, except during strenuous exercise
1	Shortness of breath when hurrying on the level or walking up a slight hill
2	Walking slower than people of the same age on the level because of breathlessness, or have to stop for breath when walking at own pace on the level
3	Stopping for breath after walking 100 meters or after a few minutes on the level
4	Too breathless to leave the house or breathlessness by dressing or undressing

Table 2 CAT Score: COPD Assessment Test

							Score
I never cough	1	2	3	4	5	cough all the time	
I have no phlegm (mucus) in my chest at all	1	2	3	4	5	My chest is completely full of phlegm (mucus)	
My chest does not feel tight at all	1	2	3	4	5	My chest feels very tight	
When I walk up a hill or one flight of stairs I am not breathless	1	2	3	4	5	When I walk up a hill or one flight of stairs I am very breathless	
I am not limited doing any activities at home	1	2	3	4	5	I am very limited doing activities at home	
I am confident leaving my home despite my lung condition	1	2	3	4	5	I am not at all confident leaving my home because of my lung condition	
I sleep soundly	1	2	3	4	5	I don't sleep soundly because of my lung condition	
I have lots of energy	1	2	3	4	5	I have not energy at all	
						Total Score	

CAT Score and resulting impact level: < 10: low; 10-20: medium; 21-30: high

Table 3 BODE Index

Variable	BODES index points			
	0	1	2	3
FEV_1 (percent of predicted)	≥ 65	50-64	36-49	≤ 35
Distance walked in 6 minutes (m)	≥ 350	250-349	150-249	≤ 149
mMRC dyspnoea scale	0-1	2	3	4
Body-mass index (kg/m^2)	> 21	≤ 21		

Approximate 4 Year Survival Interpretation: 0-2: 80%; 3-4: 67%; 5-9: 57%; 7-10: 18%

Table 4: **GOLD Classification of COPD** according to the degree of airflow limitation based on post-bronchodilator FEV_1

GOLD 1 mild	• FEV_1 > 80% predicted
GOLD 2 moderate	• 50% ≤ FEV_1 < 80% predicted
GOLD 3 severe	• 30% ≤ FEV_1< 50% predicted)
GOLD 4 very severe	• FEV_1 ≤ 30% predicted

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